



# Kongeriget Danmark

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Applicant: Novozymes A/S  
(Name and address) Krogshøjvej 36  
DK-2880 Bagsværd  
Denmark

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Title: Coated enzyme granules

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**Patent- og Varemærkestyrelsen**  
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**TITLE: COATED ENZYME GRANULES**

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**FIELD OF THE INVENTION**

The present invention relates to granules comprising a core and a coating wherein the core comprises an active compound and the coating comprises a wax composition with a wide molecular weight distribution which improves the protection against the release of active compound dust from the granule. The present invention further relates to processes for the manufacture of such coated granules.

**BACKGROUND OF THE INVENTION**

It is known to the art to incorporate active compounds such as enzymes into dry solid particles or granules and thereby protect the active compounds from inactivation and/or protect the environment from the active compounds. Such particles or granules have usually been applied to other dry products such as dry granular detergent compositions to improve their performance. Enzymes are examples of active compounds, which may be incorporated in dry solid particles or granules.

Reasons for formulating active compounds into particles, such as preparing enzyme granules include protection of the active compound by separating it from the surrounding potentially hostile environment until the moment when the active compound is to be used in an application and reduction of potentially harmful dust which may be generated from the active compound upon handling of the enzymes. Said protection of the active compound and reduction of dust formation may, in accordance with prior art be aided or improved by coating the particles.

It is known to the art to prepare granules comprising an active-containing core and various coating layers. A granule comprising active compounds typically consist of a core and a coating, where an important feature of the coating is to reduce the formation of dust when handling the granulate.

WO 96/16151 relates to enzyme granules coated with a non aqueous liquid or aqueous emulsions thereof or an unctuous mixture and an anti-caking agent.

WO 01/04279, WO 02/20746 and WO 00/01793 disclose granules comprising a lubricant.

US 4,106,991 describes a so called T-granulate which is coated with a wax.

A T-granulate coated with a wax, a triglyceride or other fat is described in WO 89/08694, EP 206,417 and in US 4,707,287.

WO 01/00042 and WO 00/47060 relates to enzyme granules for feed coated with polymers including poly ethylene glycol.

WO 01/23513 relates to liquid detergent compositions comprising solid particles comprising a solid wax matrix wherein an active is distributed.

## SUMMARY OF THE INVENTION

One object of the present invention is to provide coated granules comprising active compounds wherein the coating provides acceptable low release of active dust from the granules upon handling. A second object of the present invention is to provide coated granules comprising active compounds wherein the coating provides adequate protection of the active compound in the granules against hostile compounds in the surrounding environment. A third object of the invention is to provide coated granules comprising active compounds wherein the coating provides adequate protection against rough handling.

We have surprisingly found that coating of particles, comprising active compounds, with a wax composition comprising a wide molecular weight distribution improves Heubach dust figures of the finished granules significantly compared to ordinary granules typically coated with a wax composition comprising a narrow molecular weight distribution. We have further found that by using a wax composition comprising a wide molecular weight distribution in the coating, the coating becomes more elastic compared to granules coated with a wax composition comprising a narrow molecular weight distribution.

Hence the present invention provides granules comprising a core and a coating wherein the core comprises an active compound and wherein the coating comprises a wax composition obtainable by: mixing two or more waxes with different molecular weights wherein at least two of the waxes have a molecular weight in the range of  $0.25 \times$  the average molecular weight of the wax composition to  $2.0 \times$  the average molecular weight of the wax composition.

The Present invention further provides granules comprising a core and a coating wherein the core comprises an active compound and the coating comprises:

- a) two or more waxes and where the molecular weight of at least two of the ingoing waxes are in the range  $0.25 \times M_w$  to  $2.0 \times M_w$ , where  $M_w$  is the average molecular weight of the wax mixture, or
- a) a wax composition with a molecular weight distribution in the range of:
  - at least 10% w/w in the range  $0.25 \times M_w$  to  $0.75 \times M_w$ , and
  - at least 20% w/w in the range  $0.75 \times M_w$  to  $1.25 \times M_w$ , and
  - at least 10% w/w in the range  $1.25 \times M_w$  to  $2.0 \times M_w$ , where  $M_w$  is the average molecular weight of the wax composition, or
  - b) a wax composition with a molecular weight distribution in the range of:
    - at least 10% w/w +  $P(0.25 \times M_w \text{ to } 0.75 \times M_w)$  in the range  $0.25 \times M_w$  to  $0.75 \times M_w$ , and
    - at least 20% w/w in the range  $0.75 \times M_w$  to  $1.25 \times M_w$ , and

at least 10% w/w + P(1.25xM<sub>w</sub> to 2.0xM<sub>w</sub>) in the range 1.25xM<sub>w</sub> to 2.0xM<sub>w</sub>, where M<sub>w</sub> is the average molecular weight of the wax composition.

The invention further provides methods for preparation for preparing the coated granules of the invention, and uses of said granules.

## DETAILED DESCRIPTION OF THE INVENTION

### Definitions

A "wax" in the context of the present invention is to be construed as a polymeric material having a melting point between 25 -150 °C.

A "wax composition" of the present invention may comprise one or more waxes.

The average molecular weight "M<sub>w</sub>" in the context of the invention is for a wax composition and is defined as:

$$M_w = \sum_{i=1}^{\infty} w_i \times M_i$$

where w<sub>i</sub> is the weight fraction of each molecular weight M<sub>i</sub> present in the wax composition.

If the wax composition comprising a "wide molecular weight distribution" is obtained by mixing two or more waxes, it is described as:

A wax composition obtainable by: mixing two or more waxes with different molecular weights wherein at least two of the waxes have a molecular weight in the range of 0.25 x the average molecular weight of the wax composition to 2.0 x the average molecular weight of the wax composition.

Or it is defined as:

two or more waxes and where the average molecular weight of at least two of the ingoing waxes are in the range 0.25xM<sub>w,mix</sub> to 2.0xM<sub>w,mix</sub>, where M<sub>w,mix</sub> is the weight average molecular weight of the wax mixture, or

If the wax composition comprising a "wide molecular weight distribution" is obtained from a natural source or directly from polymerisation, or from a mixture of waxes, the wax composition comprising a "wide molecular weight distribution" in the context of the invention is defined as:

A molecular weight distribution, wherein at least 10% w/w of the molecular weight is in the range of  $0.25 \times M_w$  to  $0.75 \times M_w$ , and at least 20% w/w of the molecular weight is in the range  $0.75 \times M_w$  to  $1.25 \times M_w$  and at least 10% w/w of the molecular weight is in the range  $2.0 \times M_w$ , where  $M_w$  is the average molecular weight of the wax

5 or as:

A molecular weight distribution, wherein at least 10%w/w +  $P(0.25 \times M_w \text{ to } 0.75 \times M_w)$  in the range  $0.25 \times M_w$  to  $0.75 \times M_w$ , and at least 20%w/w in the range  $0.75 \times M_w$  to  $1.25 \times M_w$ , and at least 10% w/w +  $P(1.25 \times M_w \text{ to } 2.0 \times M_w)$  in the range  $1.25 \times M_w$  to  $2.0 \times M_w$ , where  $M_w$  is the average molecular weight of the wax.

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By a wax composition comprising a "narrow molecular weight distribution" in the context of the present invention is a wax with a narrower molecular weight distribution than defined above for a "wide molecular weight distribution". It may be a wax with a specified average molecular weight informed by the supplier when obtaining the wax commercially e.g. PEG 4000.

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The terms "particles" and "granules" in the context of the present invention are to be understood as a predominantly spherical or near spherical structure of a macromolecular size and coated particles are in the following referred to as granules.

20 The term "caking strength" in the context of the present invention is in principle the force required to break granules apart after removal of a pressure applied to a granulate, which may have caused the granules to stick together. The "caking strength" is also called the unconfined yield strength.

The "caking strength" of the present invention is measured by the following method: A container (a cylinder with an inner diameter of 64 mm, and height of 152 mm) is placed on a horizontal plate and filled to the top with granulate. A 5 kg weight fitting into the container is placed on top of the granules and removed after two minutes together with the container; if the cake of granules collapses the caking strength is zero. Weights of 100 g are placed on top of the free standing cake of granules and on top of each other until the cake collapses. The caking strength is the sum of the weights minus 50 g.

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A Poisson distributed polymer is where the fraction of molecules with  $n$  repeating units is given by

$$F(n) = e^{-m} \left[ \frac{m^n}{n!} \right]$$

where  $m$  is the average number of repeating units, and  $n$  and  $m$  are integers.

The term "substantially active free" as used herein about a coating means that there is less than 5 mg of active compound per gram coating. In practice no active compound is added to the coating feed.

## 5 Introduction

When handling solid particles comprising an active compound, one of the major problems is the formation of dust from the active compound, which may be harmful to persons handling the active compounds.

Although the active compound may be incorporated in dry solid granules as known to the art, which may inhibit the formation of active dust it is a fact that conventional granules are usually solid and brittle which makes them susceptible to damage when a strain is applied to them, which might happen during handling such as manufacture, packaging and transportation.

It is presently contemplated that dust is released when the integrity of solid particles is damaged, e.g. when a solid particle and/or its coating breaks or cracks. This may happen when the solid particle is subjected to strain such as impact or shear e.g. during handling. The strain will cause a corresponding stress building up in the solid particle to counteract the strain. Upon increasing the strain the build up of stress in the particle to counteract the strain may continue to a certain point (the yield point) depending on the particle material. However, if the strain is greater than the forces upholding the integrity of the solid particle (the yield point) the solid particle is no longer able of counteracting the strain and the strain will cause damage to the physical integrity of the solid particle, which may release dust from the solid particle. This may happen when the particle is exposed to shear or impact, especially particles with high surface roughness cause friction and the edges and corners on the surface of the particle will act as weak areas which are susceptible to breaking off as fragments of the particle or to induce breakage of the entire particle.

By coating granules comprising an active compound with a coating layer comprising a wax composition comprising a wide molecular weight distribution, the inventors have surprisingly found, it is possible to obtain much lower dust figures for the granules compared to granules coated with a wax composition comprising a narrow molecular weight distribution. It is furthermore found that by using a wax composition comprising a wide molecular weight distribution the surface of the coating becomes more smooth, less crystalline and less brittle and as a result the coating of the invention is not as susceptible to forming cracks as known coatings are, and hence the stability of the granules is improved towards hostile components in the near

environment of the granules, as the hostile components can not get in contact with the active compound through cracks in the coating.

If two or more waxes, comprising narrow molecular weight distributions, are mixed together to obtain a wax composition comprising a wide molecular weight distribution, it is preferred that the different waxes comprises molecular weights which overlap. It is more preferred that the wax composition comprising a wide molecular weight distribution in the context of the invention is an approximately uni-modal molecular weight distribution wax composition.

One way of obtaining such a wax composition comprising a wide molecular weight distribution suitable in the present invention is by mixing two or more different waxes comprising narrow molecular weight distributions. The mixing of different waxes comprising narrow molecular weight distributions may be done by the wax supplier or by the granulate manufacturer. Another way of obtaining a wax composition comprising a wide molecular weight distribution is from a manufacturer of synthetic waxes, which has been able of producing a wax composition comprising a wide molecular weight distribution during the polymerisation process or from natural sources if naturally occurring waxes can be found with a wide molecular weight distribution as defined *vide supra*.

When using a wax composition comprising a narrow molecular weight distribution as coating material, a crystalline structured coating is obtained and the crystalline coating is susceptible to cracking. By using a wax composition comprising a wide molecular weight distribution as a coating material, the inventors have found that a more amorphous coating is obtained which is not as susceptible to cracking.

When using a wax composition of low molecular weight e.g. PEG 400 the coating may become unctuous, due to the low molecular weight waxes are viscous liquids at room temperature and the granules will become sticky and unmanageable. The caking strength can tell something about how sticky the granules are. The higher the caking strength the stickier the granules are. To be able to handle the granules of the present invention the caking strength is preferably below 1000, more preferably below 800.

The inventors have further observed that when coating with a mixture of a high molecular weight wax (e.g. PEG 4000) and a low molecular weight wax (e.g. PEG 400) the coating becomes sticky and the granules become unmanageable.

Most synthetic polymer waxes are produced with a narrow molecular weight distribution. Some synthetic polymer waxes like polyethylene glycol (PEG,  $\text{H}(\text{OCH}_2\text{CH}_2)_n\text{OH}$ ) and alkylphenol ethoxylates ( $\text{RO}(\text{CH}_2\text{CH}_2\text{O})_n$  where R is an alkylphenol) are produced with a molecular weight distribution following a Poisson distribution (around the number of repeating units  $n$ ), giving a very narrow molecular weight distribution for high  $n$ -values. Other synthetic waxes like fatty alcohol ethoxylates ( $\text{RO}(\text{CH}_2\text{CH}_2\text{O})_n$  where R is a fatty alcohol) follow other distributions like e.g.

e.g. Weibull-Nycander-Gold type distributions depending on the polymeric reaction, choice of catalyst etc., but still typically resulting in a relatively narrow distribution around a mean molecular weight. References see "Chemical Fact Sheet: Nonionic Surfactants" from Orica, Sal-  
 lay, P. et al, "Molar Mass Distribution of Hydroxyethylated Aralkyl Alcohols", Periodica Poly-  
 5 technica Ser. Chem. Eng. Vol. 44, No. 2, pp. 95-110 (2000) and "Polyethylene Glycol, Product information" from Clariant

### **The coating**

The wax coating of the present invention comprises a wax composition comprising a wide molecular weight distribution

10 The wax coating may preferably constitute less than 50% by weight of the total granule. More preferably the coating may constitute less than 30% by weight of the raw granule. In some cases the wax coating may constitute less than 10% or even 5% by weight of the total granule.

The wax coating of the present invention is substantially active free.

### 15 Waxes

Suitable waxes or mixtures of waxes of the present invention may be polymeric materials hav-  
 ing a melting point of 25 to 150°C, particularly 30 to 100°C more particularly 35 to 85°C most  
 particularly 40 to 75°C. Suitable waxes are organic compounds or salts of organic compounds  
 having a melting point in the said range. The waxes are preferably in a solid state at room  
 20 temperature, 25°C, and accordingly have a melting point or a melting range (polymer waxes  
 tend to melt over a range of temperatures) above this temperature. The lower limit is preferred  
 to set a reasonable distance between the temperature at which the wax or mixture of waxes  
 starts to melt to the temperature at which the granules or compositions comprising the gran-  
 ules are usually stored, 20 to 30°C. Furthermore, difficulties are contemplated, in the manufac-  
 25 ture of the granules when the melting point of the wax or the mixture of waxes is below 30°C.

The temperature at which the wax or mixture of waxes start to melt is called  $T_{m,i}$  in the context  
 of the present invention, and the mean temperature of the melting range of a wax or a mixture  
 of waxes is called  $T_{m,m}$  in the context of the present invention. In a particular embodiment of the  
 present invention the  $T_{m,i}$  of the wax or the mixture of waxes is more than 25°C. In a more par-  
 30 ticular embodiment of the present invention the  $T_{m,i}$  of the wax or the mixture of waxes is more  
 than 30°C. In a most particular embodiment of the present invention the  $T_{m,i}$  of the wax or the  
 mixture of waxes is more than 35°C.

In a particular embodiment of the present invention the  $T_{m,m}$  of the wax or the mixture of  
 waxes is more than 30°C. In a more particular embodiment of the present invention the  $T_{m,m}$  of



the wax or the mixture of waxes is more than 35°C. In a most particular embodiment of the present invention the  $T_{m,m}$  of the wax or the mixture of waxes is more than 40°C.

The wax composition may preferably constitute at least 10 % by weight of the coating material, more preferably at least 20 % by weight of the coating material.

For some granules, e.g. granules used in the detergent industry, a preferable feature of the wax is that the wax should be water soluble or water dispersible, particularly in neutral and alkaline solution, so that when the coated particles of the invention is introduced into an aqueous solution, i.e. by diluting it with water, the wax should disintegrate and/or dissolve providing a quick release and dissolution of the active incorporated in the particles to the aqueous solution. Examples of water soluble waxes are poly ethylene glycols (PEG's). Amongst water insoluble waxes, which are dispersible in an aqueous solution are triglycerides and oils. For some granules it is preferable that they are coated with insoluble waxes e.g. feed granules.

The waxes of the invention may be any waxes, which are chemically synthesized. It may also equally well be waxes isolated from a natural source or a derivative thereof. Accordingly, the waxes of the invention may be selected from the following non limiting list of waxes.

- Poly ethylene glycols, PEG. Different PEG waxes are commercially available having different molecular sizes, wherein PEG's with low molecular sizes also have low melting points. Examples of suitable PEG's are PEG 1500, PEG 2000, PEG 3000, PEG 4000, PEG 6000, PEG 8000, PEG 9000 etc. e.g. from BASF (Pluriol E series) or from Clariant or from Ineos. Derivatives of Poly ethylene glycols.
- polypropylenes (e.g. polypropylen glycol Pluriol P series from BASF) or polyethylenes or mixtures thereof. Derivatives of polypropylenes and polyethylenes.
- Nonionic surfactants which are solid at room temperature such as ethoxylated fatty alcohols having a high level of ethoxy groups such as the Lutensol AT series from BASF, a C16-C18 fatty alcohol having different amounts of ethyleneoxide per molecule, e.g. Lutensol AT11, AT13, AT25, AT50, AT80, where the number indicate the average number of ethyleneoxide groups. Alternatively polymers of ethyleneoxide, propyleneoxide or copolymers thereof are useful, such as in block polymers, e.g. Pluronic PE 6800 from BASF. Derivatives of ethoxylated fatty alcohols.
- Waxes isolated from a natural source, such as Carnauba wax (melting point between 80-88°C), Candelilla wax (melting point between 68-70°C) and bees wax. Other natural waxes or derivatives thereof are waxes derived from animals or plants, e.g. of marine origin. Hydrogenated plant oil or animal tallow. Examples of such waxes are hydrogenated ox tallow, hy-

drogenated palm oil, hydrogenated cotton seeds and/or hydrogenated soy bean oil, wherein the term "hydrogenated" as used herein is to be construed as saturation of unsaturated carbohydrate chains, e.g. in triglycerides, wherein carbon=carbon double bonds are converted to carbon-carbon single bonds. Hydrogenated palm oil is commercially available e.g. from Hobum  
 5 Oele und Fette GmbH - Germany or Deutsche Cargill GmbH - Germany.

- Fatty acid alcohols, such as the linear long chain fatty acid alcohol NAFOL 1822 (C18, 20, 22) from Condea Chemie GMBH - Germany, having a melting point between 55-60°C. Derivatives of fatty acid alcohols.

- Mono-glycerides and/or di-glycerides, such as glyceryl stearate, wherein stearate is a  
 10 mixture of stearic and palmitic acid, are useful waxes. An example of this is Dimodan PM - from Danisco Ingredients, Denmark.

- Fatty acids, such as hydrogenated linear long chained fatty acids and derivatives of fatty acids.

- Paraffines, i.e. solid hydrocarbons.

- 15 - Micro-crystalline wax.

In further embodiments waxes which are useful in the invention can be found in C.M. McTaggart et. al., Int. J. Pharm. 19, 139 (1984) or Flanders et. al., Drug Dev. Ind. Pharm. 13, 1001 (1987) both incorporated herein by reference.

20 In a particular embodiment of the present invention the wax of the present invention is a mixture of two or more different waxes.

In a particular embodiment of the present invention the wax or waxes is selected from the group consisting of PEG, ethoxylated fatty alcohols, fatty acids, fatty acid alcohols and glycerides.

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In another particular embodiment of the present invention the waxes are chosen from synthetic waxes. In a more particular embodiment the waxes of the present invention are PEG or nonionic surfactants. In a most particular embodiment of the present invention the wax is PEG.

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Molecular weight of the wax:

Waxes are often sold specifying a molecular weight e.g. PEG 4000 where 4000 refers to the molecular weight of the PEG, but these given molecular weights are the average molecular weight of a narrow molecular weight distribution.

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In a particular embodiment of the present invention the waxes or mixture of waxes have an average molecular weight of 500 to 20,000. In a more particular embodiment of the present

invention the waxes or mixture of waxes have an average molecular weight of 750 to 15,000. In an even more particular embodiment of the present invention the waxes or mixtures of waxes have an average molecular weight of 1,000 to 10,000.

In a particular embodiment of the present invention the  $M_w$  is more than 1000. In a more particular embodiment of the present invention the  $M_w$  is more than 1200. In an even more particular embodiment of the present invention the  $M_w$  is more than 1400.

If the wax composition comprising a wide molecular weight distribution is obtained by mixing waxes with different narrow molecular weight distributions, the mixture comprises particularly at least two waxes comprising different molecular weights, where the waxes are in the range  $0.25 \times M_w$  to  $2.0 \times M_w$  where  $M_w$  is the average molecular weight of the mixture of waxes. More particularly the mixture comprises at least three waxes comprising different molecular weights, where at least two of the waxes are in the range  $0.25 \times M_w$  to  $2.0 \times M_w$ . Even more particularly the mixture comprises at least four waxes comprising different molecular weights, where at least two of the waxes are in the range  $0.25 \times M_w$  to  $2.0 \times M_w$ . Most particularly the mixture comprises at least five different waxes comprising molecular weights, where at least two of the waxes are in the range  $0.25 \times M_w$  to  $2.0 \times M_w$ .

If the wax composition comprising a wide molecular weight distribution is obtained from a natural source or directly from a polymerisation process or from mixing of waxes the granule comprises a core and a coating wherein the coating comprises a wax composition with a molecular weight distribution in the range:

at least 10% w/w in the range  $0.25 \times M_w$  to  $0.75 \times M_w$ , and

at least 20% w/w in the range  $0.75 \times M_w$  to  $1.25 \times M_w$ , and

at least 10% w/w in the range  $1.25 \times M_w$  to  $2.0 \times M_w$

or more preferred

at least 15% w/w in the range  $0.25 \times M_w$  to  $0.75 \times M_w$ , and

at least 20% w/w in the range  $0.75 \times M_w$  to  $1.25 \times M_w$ , and

at least 15% w/w in the range  $1.25 \times M_w$  to  $2.0 \times M_w$

or even more preferred

at least 20% w/w in the range  $0.25 \times M_w$  to  $0.75 \times M_w$ , and

at least 20% w/w in the range  $0.75 \times M_w$  to  $1.25 \times M_w$ , and

at least 20% w/w in the range  $1.25 \times M_w$  to  $2.0 \times M_w$

In a particular embodiment of the present invention the granule comprises a core and a coating wherein the coating comprise a wax composition with a molecular weight distribution in the range:

- at least 10%w/w +  $P(0.25M_w \text{ to } 0.75M_w)$  in the range  $0.25M_w$  to  $0.75M_w$ , and  
 at least 20%w/w in the range  $0.75M_w$  to  $1.25M_w$ , and  
 at least 10%w/w +  $P(1.25M_w \text{ to } 2.0M_w)$  in the range  $1.25M_w$  to  $2.0M_w$   
 or more preferred
- 5 at least 15% w/w +  $P(0.25M_w \text{ to } 0.75M_w)$  in the range  $0.25M_w$  to  $0.75M_w$ , and  
 at least 20% w/w in the range  $0.75M_w$  to  $1.25M_w$ , and  
 at least 15% w/w +  $P(1.25M_w \text{ to } 2.0M_w)$  in the range  $1.25M_w$  to  $2.0M_w$   
 or even more preferred  
 at least 20% w/w +  $P(0.25M_w \text{ to } 0.75M_w)$  in the range  $0.25M_w$  to  $0.75M_w$ , and
- 10 at least 20% w/w in the range  $0.75M_w$  to  $1.25M_w$ , and  
 at least 20% w/w +  $P(1.25M_w \text{ to } 2.0M_w)$  in the range  $1.25M_w$  to  $2.0M_w$

Where  $P(\text{interval})$  is defined as the weight percentage of molecules being in the interval, if the polymer is following a Poisson distribution, defined by the mean number of monomers  $m_w$  given by  $(M_w - 18 \text{ g/mole}) / (44 \text{ g/mole})$  rounded to nearest integer (i.e. the weight percentage of a Poisson distributed PEG polymer with weight average molecular weight  $M_w$  in the interval):

$P(\text{interval}) = 100 \times (F(n_k) \times M(n_k) + F(n_{k+1}) \times M(n_{k+1}) + \dots + F(n_j) \times M(n_j)) / M_w$ , where  $F(n)$  is calculated as defined in the section "Definitions" and where  $n_k$  is the number of repeating units in the molecule (as defined above for  $m_w$ ) corresponding to the lowest  $M_w$  (rounded up to the nearest integer) in the interval and  $n_j$  is the number of repeating units in the molecules corresponding to the highest  $M_w$  (rounded down to the nearest integer) in the interval.

These intervals,  $P(0.25M_w \text{ to } 0.75M_w)$ , ensure that the molecular weight distribution of the polymeric wax is significantly wider than a corresponding Poisson distributed polymer of a PEG-type.

## 25 Additional coating materials

The wax coating may further comprise additional coating materials such as fillers, binders, fibre materials, enzyme stabilizing agents, solubilising agents, crosslinking agents, suspension agents, viscosity regulating agents, light spheres, chlorine scavengers, plasticizers, pigments, salts, lubricants (such as surfactants or antistatic agents) and fragrances.

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### Fillers:

Suitable fillers are water soluble and/or insoluble inorganic salts such as finely ground alkali sulphate, alkali carbonate and/or alkali chloride, clays such as kaolin (e.g. SPESWHITE™,

English China Clay), bentonites, talcs, zeolites, chalk, calcium carbonate and/or silicates.

**Binders:**

Suitable binders are binders with a high melting point or no melting point at all and of a non waxy nature e.g. polyvinyl pyrrolidon, dextrans, polyvinylalkohol, cellulose derivatives, for example hydroxypropyl cellulose, methyl cellulose or CMC. A suitable binder is a carbohydrate binder such as Glucidex 21D™ available from Roquette Freres, France.

**Fiber materials:**

Pure or impure cellulose in fibrous form such as sawdust, pure fibrous cellulose, cotton, or other forms of pure or impure fibrous cellulose. Also, filter aids based on fibrous cellulose can be used. Several brands of cellulose in fibrous form are on the market, e.g. CEPO™ and ARBOCELL™. Pertinent examples of fibrous cellulose filter aids are ARBOCELL BFC 200™ and ARBOCELL BC 200™. Also synthetic fibres may be used as described in EP 304331 B1 and typical fibres may be made of polyethylene, polypropylene, polyester, especially nylon, polyvinylformat, poly(meth)acrylic compounds.

**Enzyme stabilizing agents:**

Enzyme stabilising or protective agents such as conventionally used in the field of granulation may be elements of the coating. Stabilising or protective agents may fall into several categories: alkaline or neutral materials, reducing agents, antioxidants and/or salts of first transition series metal ions. Each of these may be used in conjunction with other protective agents of the same or different categories. Examples of alkaline protective agents are alkali metal silicates, carbonates or bicarbonates, which provide a chemical scavenging effect by actively neutralising e.g. oxidants. Examples of reducing protective agents are salts of sulfite, thiosulfite, thiosulfate or  $\text{MnSO}_4$  while examples of antioxidants are methionine, butylated hydroxytoluene (BHT) or butylated hydroxyanisol (BHA). In particular stabilising agents may be salts of thiosulfates, e.g. sodium thiosulfate or methionine. Also enzyme stabilizers may be borates, borax, formates, di- and tricarboxylic acids and reversible enzyme inhibitors such as organic compounds with sulfhydryl groups or alkylated or arylated boric acids. Examples of boron based stabilizer may be found in WO 96/21716, whereas a preferred boron based stabilizer is 4-Formyl-Phenyl-Boronic Acid or derivatives thereof described in WO 96/41859 both disclosures incorporated herein by reference. Still other examples of useful enzyme stabilizers are gelatine, casein, Poly vinyl pyrrolidone (PVP) and powder of skimmed milk. The amounts of protective agent in the coating may be 5-40% w/w of the coating, particularly 5-30%, e.g. 10-20%.

**Solubilising agents:**

The solubility of the coating is especially critical in cases where the coated particle is a component of a detergent formulation. As is known by the person skilled in the art, many agents, through a variety of methods, serve to increase the solubility of formulations, and typical agents known to the art can be found in National Pharmacopeia's.

**Light spheres:**

Light spheres are small particles with low true density. Typically, they are hollow spherical particles with air or gas inside. Such materials are usually prepared by expanding a solid material. These light spheres may be inorganic of nature such as SCOTCHLITE™ Glass Bubbles from 3M™ (hollow glass spheres), Q-CEL® (hollow microspheres of borosilicate glass) and/or Extendospheres® (ceramic hollow spheres) available from The PQ Corporation. The light spheres may also be of organic nature such as the PM-series (plastic hollow spheres) available from The PQ Corporation. Expancel® (hollow plastic spheres) from AKZO Nobel, Luxsil® and Spherichel® from Potters Industries and/or Styrocell® from SHELL, which is spheres of polystyrene. The polystyrene of Styrocell® contains pentane which upon heating boils and expands or pops the material (the reaction is comparable to the expansion of corn seeds into popcorn) leaving a light polystyrene material of a low true density. Also polysaccharides are preferred, such as starch or derivatives thereof. Biodac® is an example of non-hollow lightweight material made from cellulose (waste from papermaking), available from GranTek Inc. These materials may be included in the granules of the invention either alone or as a mixture of different light materials.

**Crosslinking agents:**

Cross-linking agents such as enzyme-compatible surfactants, e.g. ethoxylated alcohols, especially ones with 10 to 80 ethoxy groups. These may both be found in the coating and in the core particle.

**Suspension agents:**

Suspension agents, mediators (for boosting bleach action upon dissolution of the particle in e.g. a washing application) and/or solvents may be incorporated in the coating.

**Viscosity regulating agents:**

Viscosity regulating agents may be present in the coating.

#### Plasticizers:

Plasticizers useful in coating layers in the context of the present invention include, for example: polyols such as sugars, sugar alcohols, glycerine, glycerol trimethylol propane, neopentyl glycol, triethanolamine, mono-, di- and triethylene glycol or polyethylene glycols (PEGs) having a molecular weight less than 1000; urea, phthalate esters such as dibutyl or dimethyl phthalate; thiocyanates, non-ionic surfactants such as ethoxylated alcohols and ethoxylated phosphates and water.

#### 10 Pigments:

Suitable pigments include, but are not limited to, finely divided whiteners, such as titanium dioxide or kaolin, coloured pigments, water soluble colorants, as well as combinations of one or more pigments and water soluble colorants. In case where the granules are comprising enzymes and the granules are additives for detergents, a whitening agent e.g.  $\text{TiO}_2$  can be incorporated in the granules. By adding the  $\text{TiO}_2$  at different times during the granulation process, if the granulation is performed discontinuously, at different positions in the granulator, or if the granulation is performed continuously, the  $\text{TiO}_2$  may be distributed inside the wax coating or on the surface of the wax coating or both if desired.

#### 20 Salts:

The salt may be an inorganic salt, e.g. salts of sulfate, sulfite, phosphate, phosphonate, nitrate, chloride or carbonate or salts of simple organic acids (less than 10 carbon atoms e.g. 6 or less carbon atoms) such as citrate, malonate or acetate. Examples of cations in these salt are alkali or earth alkali metal ions, although the ammonium ion or metal ions of the first transition series, such as sodium, potassium, magnesium, calcium, zinc or aluminium. Examples of anions include chloride, bromide, iodide, sulfate, sulfite, bisulfite, thiosulfate, phosphate, monobasic phosphate, dibasic phosphate, hypophosphite, dihydrogen pyrophosphate, tetraborate, borate, carbonate, bicarbonate, metasilicate, citrate, malate, maleate, malonate, succinate, lactate, formate, acetate, butyrate, propionate, benzoate, tartrate, ascorbate or gluconate. In particular alkali- or earth alkali metal salts of sulfate, sulfite, phosphate, phosphonate, nitrate, chloride or carbonate or salts of simple organic acids such as citrate, malonate or acetate may be used. Specific examples include  $\text{NaH}_2\text{PO}_4$ ,  $\text{Na}_2\text{HPO}_4$ ,  $\text{Na}_3\text{PO}_4$ ,  $(\text{NH}_4)_2\text{HPO}_4$ ,  $\text{K}_2\text{HPO}_4$ ,  $\text{KH}_2\text{PO}_4$ ,  $\text{Na}_2\text{SO}_4$ ,  $\text{K}_2\text{SO}_4$ ,  $\text{KHSO}_4$ ,  $\text{ZnSO}_4$ ,  $\text{MgSO}_4$ ,  $\text{CuSO}_4$ ,  $\text{Mg}(\text{NO}_3)_2$ ,  $(\text{NH}_4)_2\text{SO}_4$ , sodium borate, magnesium acetate and sodium citrate.

The salt may also be a hydrated salt, i.e. a crystalline salt hydrate with bound water(s) of crystallization, such as described in WO 99/32595. Examples of hydrated salts include magnesium sulfate heptahydrate ( $\text{MgSO}_4(7\text{H}_2\text{O})$ ), zinc sulfate heptahydrate ( $\text{ZnSO}_4(7\text{H}_2\text{O})$ ), copper sulfate pentahydrate ( $\text{CuSO}_4(5\text{H}_2\text{O})$ ), sodium phosphate dibasic heptahydrate ( $\text{Na}_2\text{HPO}_4(7\text{H}_2\text{O})$ ), magnesium nitrate hexahydrate ( $\text{Mg}(\text{NO}_3)_2(6\text{H}_2\text{O})$ ), sodium borate decahydrate, sodium citrate dihydrate and magnesium acetate tetrahydrate.

#### Lubricant:

As used in the present context, the term "lubricant" refers to any agent, which reduces surface friction, lubricates the surface of the granule, decreases tendency to build-up of static electricity, and/or reduces friability of the granules. Lubricants can also play a related role in improving the coating process, by reducing the tackiness of binders in the coating. Thus, lubricants can serve as anti-agglomeration agents and wetting agents. Examples of suitable lubricants are lower polyethylene glycols (PEGs), ethoxylated fatty alcohols and mineral oils. The lubricant is particularly a mineral oil or a nonionic surfactant, and more particularly the lubricant is not miscible with the other coating materials.

#### The core

The particles to be coated with the wax coating of the present invention may be of any type known to the art.

Generally all kinds of particles comprising an active compound having a size of 50 to 2000  $\mu\text{m}$  more particularly 250 to 1500  $\mu\text{m}$  even more particularly 400 to 750  $\mu\text{m}$  may be coated in accordance with the present invention.

The core particle contains the active compound. Besides of the active compound the core particle may be constructed in any way or of any material, which provides the desired functional properties of the core material, e.g. the core may consist of materials, which allows readily release of the active compounds upon introduction to an aqueous medium. In one embodiment the core particle is constructed of a particulate carrier where the active compound is absorbed into the carrier, in another embodiment the core particle is constructed of a particulate carrier where an active compound containing layer is applied on the carrier surface, optionally comprising a protecting reducing agent. There may even be additional coating within the core material providing desired functional properties of the core material. Another core particle may be the so called T-granulate wherein active compounds and granulation material is mixed to form granules incorporating the enzyme distributed throughout the core such as de-



scribed in US 4,106,991 e.g. Example 1. Any conventional methods and non-active materials may be used to prepare the core particle. Examples of known conventional cores particles and materials is, inter alia, described in, US 4,106,991 (in particular), EP 170360, EP 304332, EP 304331, EP 458849, EP 458845, WO 97/39116, WO 92/12645, WO 89/08695, WO 89/08694,  
 5 WO 87/07292, WO 91/06638, WO 92/13030, WO 93/07260, WO 93/07263, WO 96/38527, WO 96/16151, WO 97/23606, WO 01/23513, US 5,324,649, US 4,689,297, EP 206417, EP 193829, DE 4344215, DE 4322229 A, DD 263790, JP 61162185 A, JP 58179492.

As a particularly embodiment of the invention the core particle may be prepared by applying a layer of active compound onto a non-pareil or placebo carrier (active-free carrier) according to the methodology described in US 5,324,649. Optionally additional active compound  
 10 may be absorbed into the surface of the carrier.

In a particular embodiment of the invention the core particle may also comprise a protective agent or enzyme stabilizing agent as described for the coating, vide supra, particularly mixed with the active compound in suitable amounts such as 0.1-5% w/w. of the coated particle,  
 15 particularly 0.2-3% w/w, e.g. 0.3-2% w/w. The protective agent may be an antioxidant, a reducing agent or a mixture.

In a particular embodiment of the present invention the core particle May comprise an active compound e.g. an enzyme stabilized by the addition of a synthetic polymer and an antioxidant or reducing agent as described in DK PA 2002 01023

20 In one embodiment the core particle comprises an active compound dispersed in a visco-elastic liquid matrix having a  $\eta'$  and a  $\eta''$  both between 10<sup>3</sup> to 10<sup>14</sup> Pa measured in a cone-and-plate rheometer at 25°C and a sinusoidal frequencies  $\omega$  of 1 Hz. The visco-elastic liquid making up the matrix wherein the active and optionally other useful components may in principle be any material or mixtures of materials which meets the requirements for viscosity  
 25 and elasticity set for the visco-elastic core particles, as described in WO 02/28991.

In particular materials may be organic visco-elastic materials such as liquid materials comprising, consisting of or containing organic polymers and/or monomers. Materials such as carbohydrate polymers (e.g. pectins), proteins (e.g.) gelatin, sugars, glucose syrups, modified vegetable oils or mixtures thereof can be brought or formulated into a liquid state having visco-  
 30 elastic properties as described above.

Particularly a majority of the components constituting the visco-elastic liquid matrix are water soluble.

Active compound

The active compound of the invention may be any active compound or mixture of active compounds, which benefits from being separated from the environment surrounding the active compound(s). The term "active" is meant to encompass all components, which upon release  
 5 from the granule upon applying the granule of the invention in a process serve a purpose of improving the process. Suitable active compounds are those, which are either subject to deactivation and/or causing deactivation to other components in the compositions of the invention. As said the active may be present dispersed as discrete solid particles in the core particle.

The active compound may be inorganic of nature such as bleach components or organic of nature. Particular active compounds are active biological compounds which are usually very sensitive to the surrounding environment such as compounds obtainable from micro-organisms. More particular active compounds are peptides or polypeptides or proteins. Most particular are proteins such as enzymes.

15 **Enzymes:**

The enzyme in the context of the present invention may be any enzyme or combination of different enzymes. Accordingly, when reference is made to "an enzyme" this will in general be understood to include combinations of one or more enzymes.

It is to be understood that enzyme variants (produced, for example, by recombinant  
 20 techniques) are included within the meaning of the term "enzyme". Examples of such enzyme variants are disclosed, e.g., in EP 251,446 (Genencor), WO 91/00345 (Novo Nordisk), EP 525,610 (Solvay) and WO 94/02618 (Gist-Brocades NV).

The enzyme classification employed in the present specification with claims is in accordance with *Recommendations (1992) of the Nomenclature Committee of the International  
 25 Union of Biochemistry and Molecular Biology*, Academic Press, Inc., 1992.

Accordingly the types of enzymes which may appropriately be incorporated in granules of the invention include oxidoreductases (EC 1.-.-.-), transferases (EC 2.-.-.-), hydrolases (EC 3.-.-.-), lyases (EC 4.-.-.-), isomerases (EC 5.-.-.-) and ligases (EC 6.-.-.-).

Preferred oxidoreductases in the context of the invention are peroxidases (EC 1.11.1),  
 30 laccases (EC 1.10.3.2) and glucose oxidases (EC 1.1.3.4)]. An Example of a commercially available oxidoreductase (EC 1.-.-.-) is GLUZYME™ (enzyme available from Novozymes A/S). Further oxidoreductases are available from other suppliers. Preferred transferases are transferases in any of the following sub-classes:

- a) Transferases transferring one-carbon groups (EC 2.1);
- b) transferases transferring aldehyde or ketone residues (EC 2.2); acyltransferases (EC 2.3);
- c) glycosyltransferases (EC 2.4);
- d) transferases transferring alkyl or aryl groups, other than methyl groups (EC 2.5); and
- 5 e) transferases transferring nitrogenous groups (EC 2.6).

A most preferred type of transferase in the context of the invention is a transglutaminase (protein-glutamine  $\gamma$ -glutamyltransferase; EC 2.3.2.13).

Further examples of suitable transglutaminases are described in WO 96/06931 (Novo Nordisk A/S).

- 10 Preferred hydrolases in the context of the invention are: Carboxylic ester hydrolases (EC 3.1.1.-) such as lipases (EC 3.1.1.3); phytases (EC 3.1.3.-), e.g. 3-phytases (EC 3.1.3.8) and 6-phytases (EC 3.1.3.26); glycosidases (EC 3.2, which fall within a group denoted herein as "carbohydrases"), such as  $\alpha$ -amylases (EC 3.2.1.1); peptidases (EC 3.4, also known as proteases); and other carbonyl hydrolases].

- 15 In the present context, the term "carbohydrase" is used to denote not only enzymes capable of breaking down carbohydrate chains (e.g. starches or cellulose) of especially five- and six-membered ring structures (i.e. glycosidases, EC 3.2), but also enzymes capable of isomerizing carbohydrates, e.g. six-membered ring structures such as D-glucose to five-membered ring structures such as D-fructose.

- 20 Carbohydrases of relevance include the following (EC numbers in parentheses):

- $\alpha$ -amylases (EC 3.2.1.1),  $\beta$ -amylases (EC 3.2.1.2), glucan 1,4- $\alpha$ -glucosidases (EC 3.2.1.3), endo-1,4-beta-glucanase (cellulases, EC 3.2.1.4), endo-1,3(4)- $\beta$ -glucanases (EC 3.2.1.6), endo-1,4- $\beta$ -xylanases (EC 3.2.1.8), dextranases (EC 3.2.1.11), chitinases (EC 3.2.1.14), polygalacturonases (EC 3.2.1.15), lysozymes (EC 3.2.1.17),  $\beta$ -glucosidases (EC 3.2.1.21),  $\alpha$ -galactosidases (EC 3.2.1.22),  $\beta$ -galactosidases (EC 3.2.1.23), amylo-1,6-glucosidases (EC 3.2.1.33), xylan 1,4- $\beta$ -xylosidases (EC 3.2.1.37), glucan endo-1,3- $\beta$ -D-glucosidases (EC 3.2.1.39),  $\alpha$ -dextrin endo-1,6- $\alpha$ -glucosidases (EC 3.2.1.41), sucrose  $\alpha$ -glucosidases (EC 3.2.1.48), glucan endo-1,3- $\alpha$ -glucosidases (EC 3.2.1.59), glucan 1,4- $\beta$ -glucosidases (EC 3.2.1.74), glucan endo-1,6- $\beta$ -glucosidases (EC 3.2.1.75), arabinan endo-1,5- $\alpha$ -L-arabinosidases (EC 3.2.1.99), lactases (EC 3.2.1.108), chitosanases (EC 3.2.1.132) and xylose isomerases (EC 5.3.1.5).
- 25
- 30

Examples of commercially available proteases (peptidases) include KANNASE™, EVERLASE™, ESPERASE™, ALCALASE™, NEUTRASE™, DURAZYM™, SAVINASE™, PYRASE™, Pancreatic Trypsin NOVO (PTN), BIO-FEED™ PRO and CLEAR-LENS™ PRO (all available from Novozymes A/S).

- 5 Other commercially available proteases include MAXATASE™, MAXACAL™, MAXAPEM™, OPTICLEAN™ and PURAFECT™ (available from Genencor International Inc. or DSM).

Examples of commercially available lipases include LIPOPRIME™ LIPOLASE™, LIPOLASE™ Ultra, LIPOZYME™, PALATASE™, NOVOZYM™ 435 and LECITASE™ (all  
10 available from Novozymes A/S).

Other commercially available lipases include LUMAFast™ (*Pseudomonas mendocina* lipase from Genencor International Inc.); LIPOMAX™ (*Ps. pseudoalcaligenes* lipase from DSM/Genencor Int. Inc.; and *Bacillus* sp. lipase from Genencor enzymes. Further lipases are available from other suppliers.

- 15 Examples of commercially available carbohydrases include ALPHA-GAL™, BIO-FEED™ Alpha, BIO-FEED™ Beta, BIO-FEED™ Plus, BIO-FEED™ Plus, NOVOZYME™ 188, CELLUCLAST™, CELLUSOFT™, CEREMYL™, CITROZYM™, DENIMAX™, DEZYME™, DEXTROZYME™, FINIZYM™, FUNGAMYL™, GAMANASE™, GLUCANEX™, LACTOZYME™, MALTOGENASE™, PENTOPAN™, PECTINEX™, PROMOZYME™, PULPZYME™, NOVA-  
20 MYL™, TERMAMYL™, AMG™ (Amyloglucosidase Novo), MALTOGENASE™, SWEETZYME™ and AQUAZYM™ (all available from Novozymes A/S). Further carbohydrases are available from other suppliers.

#### Additional coatings

- The granule of the present invention may comprise one or more additional coatings besides  
25 the wax coating.

Additional coatings may be present either in between the core and the wax coating or as a layer outside the wax coating.

- Conventional coatings and methods as known to the art may suitably be used, such as the coatings described in Danish PA 2002 00473, Danish PA 2001 01930, WO 89/08694, WO  
30 89/08695, 270 608 B1 and/or WO 00/01793. Other examples of conventional coating materials may be found in US 4,106,991, EP 170360, EP 304332, EP 304331, EP 458849, EP 458845, WO 97/39116, WO 92/12645A, WO 89/08695, WO 89/08694, WO 87/07292, WO 91/06638, WO

92/13030, WO 93/07260, WO 93/07263, WO 96/38527, WO 96/16151, WO 97/23606, WO 01/25412, WO 02/20746, WO 02/28369, US 5879920, US 5,324,649, US 4,689,297, US 6,348,442, EP 206417, EP 193829, DE 4344215, DE 4322229 A, DE 263790, JP 61162185 A and/or JP 58179492.

5 In a particular embodiment of the present invention the additional coating layer is a salt coating as described in DK 02/00885, hereby incorporated by reference

Conventional coating materials may be used including the materials mentioned under the section "The coating".

10 In a particular embodiment of the present invention the coating layers around the core unit have a thickness such as the ratio between the diameter of the granule and the diameter of the core being at least 1.1 as described in WO 01/25412, hereby incorporated by reference.

### **Process for preparing granules**

#### The wax coating:

15 In one embodiment of the present invention the process of preparing the granules of the present invention comprise contacting a particle comprising an active compound with a coating, wherein the coating comprises a wax composition obtainable by:

20 mixing two or more waxes with different molecular weights wherein at least two of the waxes have a molecular weight in the range of  $0.25 \times$  the average molecular weight of the wax composition to  $2.0 \times$  the average molecular weight of the wax composition.

In another embodiment of the present invention the process of preparing the granules of the present invention comprise contacting a particle comprising an active compound with a coating, wherein the coating comprises:

25 a) two or more waxes and where the molecular weight of at least two of the ingoing waxes are in the range  $0.25 \times M_w$  to  $2.0 \times M_w$ , where  $M_w$  is the average molecular weight of the wax mixture, or

b) a wax with a molecular weight distribution in the range of:  
 at least 10% w/w in the range  $0.25 \times M_w$  to  $0.75 \times M_w$ , and  
 at least 20% w/w in the range  $0.75 \times M_w$  to  $1.25 \times M_w$ , and  
 30 at least 10% w/w in the range  $1.25 \times M_w$  to  $2.0 \times M_w$ , where  $M_w$  is the mean molecular weight of the wax, or

- c) a wax with a molecular weight distribution in the range of:  
 at least 10%w/w + P(0.25xM<sub>w</sub> to 0.75xM<sub>w</sub>) in the range 0.25xM<sub>w</sub> to 0.75xM<sub>w</sub>, and  
 at least 20%w/w in the range 0.75xM<sub>w</sub> to 1.25xM<sub>w</sub>, and  
 at least 10%w/w + P(1.25xM<sub>w</sub> to 2.0xM<sub>w</sub>) in the range 1.25xM<sub>w</sub> to 2.0xM<sub>w</sub>, where M<sub>w</sub> is  
 5 the mean molecular weight of the wax.

In a particular embodiment of the present invention the contacting of the particle with the wax coating is taking place in a coating chamber.

10 In a particular embodiment of the present invention the contacting of the particle with the wax coating is taking place in a fluid bed apparatus or in a mixer apparatus.

The waxes used in the wax coating are always used in liquid form in the coating process; the waxes are therefore either dissolved or dispersed in water or melted. If the waxes are dispersed in water, the water is removed during a drying step. If no water is used in the coating, usually no drying is needed. In this case the coating material only comprises melted wax,  
 15 only cooling is needed to solidify the granules. In most cases, drying or cooling is usually carried out in a fluid bed. A flow conditioner or anticaking agent may be added to the granulate either before or after the cooling step, e.g. fumed silica, for instance the commercial products AEROSIL or CABOSIL.

20 The coating may be applied to the core particles using any conventional coating method including those preparation methods mentioned vide infra under the section "Preparing core particles. In a particular embodiment of the present invention the coating is applied in a mixer, in a fluid bed or in a pan or drum coater. In a particular embodiment of the fluid bed coating process, the fluidised core particles are sprayed with a solution containing the coating material(s) and the coating is deposited on the surface of the core particles by evaporating the  
 25 solution solvent, see e.g. US 6,136,772.

If the coating is applied to the core particles in a fluid bed the temperature of the coating will typically be between 0 to 100°C, particularly between 10 to 90°C, more particularly between 10 to 80°C or most particularly between 10 to 70°C. The inlet air-temperature in the fluid  
 30 bed will typically be between 30 to 200°C, particularly between 40 to 150°C, more particularly between 40 to 120°C.

As the coating comprises a wax and if it is applied in a mixer the mixer temperature should be higher than the melting temperature of the wax. This will typically lie between 30 to 100°C.

35 The coating process can take place in any of the known types of mixing granulators, drum granulators, pan granulators or modifications of these. If a mixing granulator is used, for

example a mixing drum from the German Company Gebr. Lodige Maschinen G.m.b.H, it is preferred that small rotating knives are mounted in the granulator in order to compact the granules.

5 The granulation may be performed as described in US patent 4,106,991 and WO 92/12645 (hereby incorporated as references).

The coated granulates may be further coated with additional layers as mentioned vide supra, e.g. a colored layer such as  $\text{TiO}_2$  or lubricated, or the particle comprising the active compound may be coated with one or more additional layers before applying the wax coating.

#### 10 Preparing core particles

Methods for preparing core particles include those disclosed in the above mentioned references, and may include but are not limited to preparation methods like spray drying, layering, absorption, crystallization, precipitation extrusion, pelletizing, prilling and mixer granulation.

15

Methods for preparing a visco-elastic liquid core particle include those described in WO 02/28991.

#### **Compositions comprising the coated particle and their application**

20 The invention also relates to compositions comprising the granules of the invention. The composition may be any composition, but particularly the compositions are well suited for use in the pharmaceutical industry, the detergent industry, the feed and fodder industry and in the baking industry. Accordingly the compositions may be detergent compositions, a feed composition, a fodder composition, a baking composition or an additive to be incorporated in such compositions.

25 The granules may further be used in fertilizer compositions or as a fertilizer.

#### Feed/Fodder

In a particular embodiment of the present invention the granules of the present invention are useful in animal feed compositions.

In a particular embodiment of the present invention the granules of the present  
30 invention are useful in fodder compositions.

Baking

In a special embodiment of the invention we have found that our development of coated granules comprising an active is useful in the baking industry. In a particular embodiment of the present invention the granules are used as dough improver.

5           Within the flour mill and the baking industry the use of active compounds, such as enzymes, is well established. Accordingly the invention provides baking compositions comprising the coated granules of the invention, in particular dough improver compositions or flour compositions comprising the dough improver.

          When using enzymes in the baking industry certain enzyme activities are preferred.  
10          Flour has varying content of amylases leading to differences in the baking quality. Addition of amylases can be necessary in order to standardize the flour. Amylases and pentosanases generally provide sugar for the yeast fermentation, improve the bread volume, retard retro gradation, and decrease the staling rate and stickiness that results from pentosan gums. Examples of carbohydrases are given below.

15           Certain maltogenic amylases e.g. Novamyl<sup>™</sup> can be used for prolonging the shelf life of bread for two or more days without causing gumminess in the product. Selectively modifies the gelatinized starch by cleaving from the non-reducing end of the starch molecules, low molecular weight sugars and dextrins. The starch is modified in such a way that retro gradation is less likely to occur. The produced low-molecular-weight sugars improve the baked goods water retention  
20          capacity without creating the intermediate-length dextrins that result in gumminess in the finished product. The enzyme is inactivated during bread baking, so it can be considered a processing aid, which does not have to be declared on the label.

          The bread volume can be improved by fungal  $\alpha$ -amylases, which further provide good and uniform structure of the bread crumb.

25          Said  $\alpha$ -amylases are endoenzymes that produce maltose, dextrins and glucose. Cereal and some bacterial  $\alpha$ -amylases are inactivated at temperatures above the gelatinization temperature of starch, therefore when added to wheat dough it results in a low bread volume and a sticky bread interior. Fungamyl has the advantage of being thermolabile and is inactivated just below the gelatinization temperature.

30           Enzyme preparations containing a number of pentosanase and hemicellulase activities can improve the handling and stability of the dough, and improves the freshness, the crumb structure and the volume of the bread.



By hydrolysing the pentosans fraction in flour, it will lose a great deal of its water-binding capacity, and the water will then be available for starch and gluten. The gluten becomes more pliable and extensible, and the starch gelatinize more easily. Pentosanases can be used in combination with or as an alternative to emulsifiers.

## 5 Detergents

The coated particles of the invention may be added to and thus become a component of a detergent composition.

The detergent composition of the invention may for example be formulated as laundry detergent composition for hand or machine washings including a cleaning additive composition suitable for pre-treatment of stained fabrics or a fabric softener composition, or a detergent composition for use in general household hard surface cleaning operations, or a composition for hand or machine dishwashing operations.

In a specific aspect, the invention provides a detergent additive comprising the coated particles of the invention. The detergent additive as well as the detergent composition may comprise one or more other enzymes such as a protease, a lipase, a cutinase, an amylase, a carbohydrase, a cellulase, a pectinase, a mannanase, an arabinase, a galactanase, a xylanase, an oxidase, e.g., a laccase, and/or a peroxidase.

In general the properties of the chosen enzyme(s) should be compatible with the selected detergent, (i.e. pH-optimum, compatibility with other enzymatic and non-enzymatic ingredients, etc.), and the enzyme(s) should be present in effective amounts.

Proteases: Suitable proteases include those of animal, vegetable or microbial origin. Microbial origin is preferred. Chemically modified or protein engineered mutants are included. The protease may be a serine protease or a metallo protease, preferably an alkaline microbial protease or a trypsin-like protease. Examples of alkaline proteases are subtilisins, especially those derived from *Bacillus*, e.g., subtilisin Novo, subtilisin Carlsberg, subtilisin 309, subtilisin 147 and subtilisin 168 (described in WO 89/06279). Examples of trypsin-like proteases are trypsin (e.g. of porcine or bovine origin) and the *Fusarium* protease described in WO 89/06270 and WO 94/25583.

Examples of useful proteases are the variants described in WO 92/19729, WO 98/20115, WO 98/20116, and WO 98/34946, especially the variants with substitutions in one or more of the following positions: 27, 36, 57, 76, 87, 97, 101, 104, 120, 123, 167, 170, 194, 206, 218, 222, 224, 235 and 274.

Preferred commercially available protease enzymes include EVERLASE™, OVOZYME™, SAVOZYME™, ALCALASE™, SAVINASE™, PRIMASE™, DURALASE™, ESPERASE™, AND KANNASE™ (Novozymes A/S), MAXATASE™, MAXACAL™, MAXAPEM™, PROPERASE™, PURAFECT™, PURAFECT OXP™, FN2™, and FN3™, FN4™ (Genencor International Inc.).

5           Lipases: Suitable lipases include those of bacterial or fungal origin. Chemically modified or protein engineered mutants are included. Examples of useful lipases include lipases from *Humicola* (synonym *Thermomyces*), e.g. from *H. lanuginosa* (*T. lanuginosus*) as described in EP 258 068 and EP 305 216 or from *H. insolens* as described in WO 96/13580, a *Pseudomonas* lipase, e.g. from *P. alcaligenes* or *P. pseudoalcaligenes* (EP 218 272), *P. cepacia* (EP 331 376), *P. stutzeri* (GB 1,372,034), *P. fluorescens*, *Pseudomonas* sp. strain SD 705 (WO 95/06720 and WO 10 96/27002), *P. wisconsinensis* (WO 96/12012), a *Bacillus* lipase, e.g. from *B. subtilis* (Dartois et al. (1993), *Biochimica et Biophysica Acta*, 1131, 253-360), *B. stearothermophilus* (JP 64/744992) or *B. pumilus* (WO 91/16422).

Other examples are lipase variants such as those described in WO 92/05249, WO 15 94/01541, EP 407 225, EP 260 105, WO 95/35381, WO 96/00292, WO 95/30744, WO 94/25578, WO 95/14783, WO 95/22615, WO 97/04079 and WO 97/07202.

Preferred commercially available lipase enzymes include LIPOLASE™ and LIPOLASE ULTRA™ (Novozymes A/S).

20           Amylases: Suitable amylases ( $\alpha$  and/or  $\beta$ ) include those of bacterial or fungal origin. Chemically modified or protein engineered mutants are included. Amylases include, for example,  $\alpha$ -amylases obtained from *Bacillus*, e.g. a special strain of *B. licheniformis*, described in more detail in GB 1,296,839.

Examples of useful amylases are the variants described in WO 94/02597, WO 94/18314, WO 96/23873, and WO 97/43424, especially the variants with substitutions in one or more of the 25 following positions: 15, 23, 105, 106, 124, 128, 133, 154, 156, 181, 188, 190, 197, 202, 208, 209, 243, 264, 304, 305, 391, 408, and 444.

Commercially available amylases are DURAMYL™, TERMAMYL™, FUNGAMYL™ and BAN™ (Novozymes A/S), RAPIDASE™, PURASTAR™ and PURASTAR OXAM™ (from Genencor International Inc.).

30           Cellulases: Suitable cellulases include those of bacterial or fungal origin. Chemically modified or protein engineered mutants are included. Suitable cellulases include cellulases from the

genera *Bacillus*, *Pseudomonas*, *Humicola*, *Fusarium*, *Thielavia*, *Acremonium*, e.g. the fungal cellulases produced from *Humicola insolens*, *Myceliophthora thermophila* and *Fusarium oxysporum* disclosed in US 4,435,307, US 5,648,263, US 5,691,178, US 5,776,757 and WO 89/09259.

Especially suitable cellulases are the alkaline or neutral cellulases having colour care  
 5 benefits. Examples of such cellulases are cellulases described in EP 0 495 257, EP 0 531 372, WO 96/11262, WO 96/29397, WO 98/08940. Other examples are cellulase variants such as those described in WO 94/07998, EP 0 531 315, US 5,457,046, US 5,686,593, US 5,763,254, WO 95/24471, WO 98/12307 and PCT/DK98/00299.

Commercially available cellulases include CELLUZYME™, and CAREZYME™ (No-  
 10 vozymes A/S), CLAZINASE™, and PURADAX HA™ (Genencor International Inc.), and KAC-500(B)™ (Kao Corporation).

Peroxidases/Oxidases: Suitable peroxidases/oxidases include those of plant, bacterial or fungal origin. Chemically modified or protein engineered mutants are included. Examples of useful  
 15 peroxidases include peroxidases from *Coprinus*, e.g. from *C. cinereus*, and variants thereof as those described in WO 93/24618, WO 95/10602, and WO 98/15257.

Commercially available peroxidases include GUARDZYME™ (Novozymes A/S).

Mannanase: Suitable mannanases include MANNAWAY™(Novozymes A/S).

The detergent enzyme(s) may be included in a detergent composition by adding separate  
 20 additives containing one or more enzymes, or by adding a combined additive comprising all of these enzymes. A detergent additive of the invention, i.e. a separate additive or a combined additive, may be formulated so as to contain one or more of the particles of the invention comprising different enzymes.

The detergent composition of the invention may be in any convenient dry form, e.g., a bar,  
 25 a tablet, a powder, a granule or a paste. It may also be a liquid detergent, in particular non-aqueous liquid detergent.

The detergent composition comprises one or more surfactants, which may be non-ionic  
 including semi-polar and/or anionic and/or cationic and/or zwitterionic. The surfactants are typically present at a level of from 0.1% to 60% by weight.

When included therein the detergent will usually contain from about 1% to about 40% of  
 30 an anionic surfactant such as linear alkylbenzenesulfonate, alpha-olefinsulfonate, alkyl sulfate

(fatty alcohol sulfate), alcohol ethoxysulfate, secondary alkanesulfonate, alpha-sulfo fatty acid methyl ester, alkyl- or alkenylsuccinic acid or soap.

When included therein the detergent will usually contain from about 0.2% to about 40% of a non-ionic surfactant such as alcohol ethoxylate, nonylphenol ethoxylate, alkylpolyglycoside, alkyl-  
 5 dimethylamineoxide, ethoxylated fatty acid monoethanolamide, fatty acid monoethanolamide, polyhydroxy alkyl fatty acid amide, or N-acyl N-alkyl derivatives of glucosamine ("glucamides").

The detergent may contain 0-65 % of a detergent builder or complexing agent such as zeolite, diphosphate, triphosphate, phosphonate, carbonate, citrate, nitrilotriacetic acid, ethyl-  
 10 enediaminetetraacetic acid, diethylenetriaminepentaacetic acid, alkyl- or alkenylsuccinic acid, soluble silicates or layered silicates (e.g. SKS-6 from Hoechst).

The detergent may comprise one or more polymers. Examples are carboxymethylcellulose, poly(vinylpyrrolidone), poly (ethylene glycol), poly(vinyl alcohol), poly(vinylpyridine-N-oxide), poly(vinylimidazole), polycarboxylates such as polyacrylates, maleic/acrylic acid copolymers and lauryl methacrylate/acrylic acid copolymers.

15 The detergent may contain a bleaching system, which may comprise a H<sub>2</sub>O<sub>2</sub> source such as perborate or percarbonate, which may be combined with a peracid-forming bleach activator such as tetraacetylenediamine or nonanoyloxybenzenesulfonate. Alternatively, the bleaching system may comprise peroxyacids of e.g. the amide, imide, or sulfone type.

The enzyme(s) of the detergent composition of the invention may be stabilized using conventional stabilizing agents, e.g., a polyol such as propylene glycol or glycerol, a sugar or sugar  
 20 alcohol, lactic acid, boric acid, or a boric acid derivative, e.g., an aromatic borate ester, or a phenyl boronic acid derivative such as 4-formylphenyl boronic acid, and the composition may be formulated as described in e.g. WO 92/19709 and WO 92/19708.

The detergent may also contain other conventional detergent ingredients such as e.g. fabric  
 25 conditioners including clays, foam boosters, suds suppressors, anti-corrosion agents, soil-suspending agents, anti-soil redeposition agents, dyes, bactericides, optical brighteners, hydro-tropes, tarnish inhibitors, or perfumes.

It is at present contemplated that in the detergent compositions any enzyme, may be added in an amount corresponding to 0.01-100 mg of enzyme protein per litre of wash liquor,  
 30 preferably 0.05-5 mg of enzyme protein per litre of wash liquor, in particular 0.1-1 mg of enzyme protein per litre of wash liquor.

The enzyme of the invention may additionally be incorporated in the detergent formulations disclosed in WO 97/07202, which is hereby incorporated as reference.

## EXAMPLES

### Example 1

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Interval 1: From  $0.25 \times M_{w,mix}$  to  $0.75 \times M_{w,mix}$

Interval 2: From  $0.75 \times M_{w,mix}$  to  $1.25 \times M_{w,mix}$

Interval 3: From  $1.25 \times M_{w,mix}$  to  $2.00 \times M_{w,mix}$

Examples of mixtures (calculated from Poisson distributions of polymers)

PEG mixtures	P1	P2	P3	P4	P5	P6	P7
PEG-400	10%						
PEG-1000					2%	10%	9%
PEG-2000				1%	15%	15%	18%
PEG-3000			9%	24%	25%	25%	22%
PEG-4000	90%	100%	90%	62%	30%	40%	29%
PEG-6000			1%	13%	28%	10%	18%
PEG-8000							4%
$M_{w,mix}$	3660	4022	3949	4012	3956	3356	3673
$n_{w,mix}$	83	91	89	91	89	76	83
Int. 1	0%	1%	4%	13%	26%	24%	29%
Int. 2	81%	98%	93%	74%	45%	52%	44%
Int. 3	9%	1%	3%	13%	28%	21%	21%
Visual evaluation of crystalline structure	Large crystals	Large crystals	Large crystals	Medium Crystals/ amorph	Medium Crystals/ Amorph	Small Amorph	Small Amorph
Surface evaluation	Wet/sticky	Dry	Dry	Dry	Dry	Dry	Dry

The crystalline structure (given by visual inspection of the size of the crystal patterns on the surface of solidified (cooled to room temperature) wax mixture) is less pronounced (more amorphous) with increasing molecular weights. Adding a liquid (at room temperature) wax to a solid (example P1) gives a wet and sticky surface (also making it difficult to evaluate crystal patterns).

### Example 2

Two batches (one in a 130 liter Lödige mixer and one produced in a 600 liter Lödige mixer) of uncoated Savinase granulate with an approximate activity of 15 KNPU/g were produced as described in US 4,106,991 example 1 with the following exceptions:

- Finely grinded sodium sulfate was used instead of sodium chloride as filler material
- The enzyme concentrate (added as a liquid) contained also a carbohydrate binder (Avedex W80 dextrin)

The granulates were sieved in the fraction 250 to 850 microns and coated (in a 5 liter Lödige mixer) with 23.75% coating (relative to the uncoated material) as described in US 4,109,991 example 22 with the following coating compositions:

Reference coating: 41% PEG-4000, 41% Titan dioxide and 18% Calcium carbonate

PEG-mix coating: 41% Titan dioxide, 18% Calcium carbonate and 41% PEG-mixture, P6 from example 1, comprising: 10% PEG-1000, 15% PEG-2000, 25% PEG-3000, 40% PEG-4000, 10% PEG-6000.

All granulates were finally powdered with 0.75% Kaolin

The dust from the four granulates were tested using the conventional Heubach attrition method which is known to the art, (see e.g. WO 96/16151 and WO 93/07263), measuring both the total dust created (as mg dust per 20 g granulate) and the enzyme dust (as nanogram protein per g granulate).

Granulate	Total dust as mg per 20 gram granulate	Active dust as ng Savinase protein per gram granulate
Reference coating on 130 liter Lödige granulate	74.9	1374
PEG-mix coating on 130 liter Lödige granulate	0.0	13
Reference coating on 600 liter Lödige granulate	21.5	3090
PEG-mix coating on 600 liter Lödige granulate	0.1	156

It is clearly seen that the PEG-mix coating reduces the dust significantly.

**CLAIMS**

1. A granule comprising a core and a coating wherein the core comprises an active compound and wherein the coating comprises a wax composition obtainable by:

5 mixing two or more waxes with different molecular weights wherein at least two of the waxes have a molecular weight in the range of  $0.25 \times$  the average molecular weight of the wax composition to  $2.0 \times$  the average molecular weight of the wax composition.

2. A granule comprising a core and a coating wherein the core comprises an active compound and the coating comprises:

10 a) two or more waxes and where the molecular weight of at least two of the ingoing waxes are in the range  $0.25M_w$  to  $2.0M_w$ , where  $M_w$  is the average molecular weight of the wax mixture, or

b) a wax composition with a molecular weight distribution in the range of:  
at least 10% w/w in the range  $0.25M_w$  to  $0.75M_w$ , and  
at least 20% w/w in the range  $0.75M_w$  to  $1.25M_w$ , and  
15 at least 10% w/w in the range  $1.25M_w$  to  $2.0M_w$ , where  $M_w$  is the weight average molecular weight of the wax composition, or

c) a wax composition with a molecular weight distribution in the range of:  
at least 10%w/w + P( $0.25M_w$  to  $0.75M_w$ ) in the range  $0.25M_w$  to  $0.75M_w$ , and  
at least 20%w/w in the range  $0.75M_w$  to  $1.25M_w$ , and  
20 at least 10%w/w + P( $1.25M_w$  to  $2.0M_w$ ) in the range  $1.25M_w$  to  $2.0M_w$ , where  $M_w$  is the weight average molecular weight of the wax composition.

3. The granule according to any of the claims 1 or 2, wherein the  $T_{m,i}$  of the waxes is at least 25°C.

4. The granule according to any of the claims 1 to 3, wherein  $T_{m,i}$  of the wax composition  
25 is at least 30°C.



5. The granule according to any of the claims 1 to 4, wherein  $T_{m,i}$  of the wax composition is at least 35°C.
6. The granule according to any of the claims 1 to 5 wherein  $T_{m,m}$  of the wax composition is at least 30°C.
- 5 7. The granule according to any of the claims 1 to 6, wherein  $T_{m,m}$  of the wax composition is at least 35°C.
8. The granule according to any of the claims 1 to 7, wherein  $T_{m,m}$  of the wax composition is at least 40°C.
9. The granule according to any of the claims 1 to 8, wherein  $M_w$  is more than 1000.
- 10 10. The granule according to any of the claims 1 to 9, wherein  $M_w$  is more than 1200.
11. The granule according to any of the claims 1 to 10, wherein  $M_w$  is more than 1400.
12. The granule according to any of the claims 1 to 11, wherein the waxes are selected from the group consisting of PEG, ethoxylated fatty alcohols, fatty acids, fatty acid alcohols and glycerides.
- 15 13. The granule according to any of the claims 1 to 12, wherein the granules have a caking strength of less than 1000.
14. The granule according to any of the claims 1 to 13, wherein the active compound is a protein.
15. The granule according to claim 14, wherein the protein is an enzyme.
- 20 16. A process for preparing the granule according to claim 1, comprising contacting a particle comprising an active compound with a coating, wherein the coating comprises: a wax composition obtainable by:

mixing two or more waxes with different molecular weights wherein at least two of the waxes have a molecular weight in the range of  $0.25 \times$  the average molecular weight of the wax composition to  $2.0 \times$  the average molecular weight of the wax composition.

17. A process for preparing the granule according to claim 1, comprising contacting a particle comprising an active compound with a coating, wherein the coating comprises
  - a) two or more waxes and where the molecular weight of at least two of the ingoing waxes are in the range  $0.25M_w$  to  $2.0M_w$ , where  $M_w$  is the average molecular weight of the wax mixture, or
  - b) a wax with a molecular weight distribution in the range of:
    - at least 10% w/w in the range  $0.25M_w$  to  $0.75M_w$ , and
    - at least 20% w/w in the range  $0.75M_w$  to  $1.25M_w$ , and
    - at least 10% w/w in the range  $1.25M_w$  to  $2.0M_w$ , where  $M_w$  is the mean molecular weight of the wax, or
  - c) a wax with a molecular weight distribution in the range of:
    - at least 10%w/w +  $P(0.25M_w \text{ to } 0.75M_w)$  in the range  $0.25M_w$  to  $0.75M_w$ , and
    - at least 20%w/w in the range  $0.75M_w$  to  $1.25M_w$ , and
    - at least 10%w/w +  $P(1.25M_w \text{ to } 2.0M_w)$  in the range  $1.25M_w$  to  $2.0M_w$ , where  $M_w$  is the mean molecular weight of the wax.
18. The process according to claim 16 or 17, wherein said contacting of the particle with a coating is taking place in a coating chamber.
19. The process according to claim 16 or 17, wherein said contacting of the particle with a coating is taking place in a fluid bed apparatus or in a mixer apparatus.
20. The use of any of the granules according to claim 1 to 15, in feed compositions for animals.
21. The use of any of the granules according to any of the claims 1 to 15, in fodder compositions for animals.
22. The use of any of the granules according to claim 1 to 15, as a dough improver.

23. The use of any of the granules according to claim 1 to 15, within the detergent industry.
24. The use of any of the granules according to any of the claims 1 to 15, in fertilizer compositions.
25. The use of any of the granules according to any of the claims 1 to 15, in  
5 pharmaceutical compositions.

## **ABSTRACT**

The present invention relates to granules comprising a core and a coating, wherein the core comprises an active compound and the coating comprises a wax composition with a wide molecular weight distribution.

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